

General

deutetrabenazine for the treatment of chorea associated with Huntington's disease

Harshit Gupta¹, Wil Perkins², Cain Stark³, Sathya Kikkeri⁴, Juyeon Kakazu⁵, Adam D. Kaye⁶, Alan D. Kaye⁷

¹ School of Medicine, David Geffen School of Medicine, ² School of Medicine, Louisiana State University Shreveport School of Medicine, ³ School of Medicine, Medical College of Wisconsin, ⁴ School of Osteopathic Medicine, Alabama College of Osteopathic Medicine, ⁵ School of Medicine, Georgetown University School of Medicine, ⁶ School of Pharmacy, Thomas J. Long School of Pharmacy and Health Sciences, ⁷ Anesthesiology, Louisiana State University Shreveport

Keywords: Deutetrabenazine, Huntington's disease, Chorea, VMAT2, neurodegenerative

<https://doi.org/10.52965/001c.36040>

Health Psychology Research

Vol. 10, Issue 5, 2022

This is a comprehensive review of the literature regarding the use of Deutetrabenazine in treating chorea associated with Huntington's disease. Unfortunately, treatment has been limited for many aspects of this neurodegenerative disease. The present investigation presents the background, evidence, and indications for the use Deutetrabenazine in the setting of Huntington's disease. Huntington's disease is characterized by a variety of motor, psychiatric, and cognitive symptoms with chorea being one of the more notable ones. Chorea is a movement disorder present in multiple neurologic diseases that causes involuntary and irregular muscle movements theorized to be stemming from high dopamine levels. Deutetrabenazine is thought to function as an inhibitor of the VMAT2 vesicular monoamine transporter resulting in decreased monoamine release, including dopamine, in the synaptic cleft which has a therapeutic effect in management of chorea. This drug was approved by the FDA in 2017 with a specific indication for tardive dyskinesia and choreiform movement in Huntington's disease. Currently, there is no definitive treatment for Huntington's disease. Thus, management is primarily focused on symptom management with the use of a variety of pharmaceutical agents. Chorea is one of the many manifestations that significantly alter the quality of life of many patients. Deutetrabenazine is a promising new option for the treatment of chorea in the setting of Huntington's disease. Although studies so far have displayed mixed results, further research, including head-to-head studies, is necessary to elucidate the true potential of this drug.

INTRODUCTION

Huntington's disease (HD) is an autosomal-dominant, progressive neurodegenerative disorder characterized by a triad of motor, psychiatric and cognitive symptoms that typically onset in middle-aged individuals, although it can present on a spectrum of ages depending on the extent of the cytosine-adenosine-guanine (CAG) repeat mutation in the huntingtin-encoding gene. Specifically, the age of onset is inversely related to the number of CAG repeats present with each subsequent generation being diagnosed at earlier ages related to the phenomenon of anticipation whereby the number of repeats is increased in each generation.¹ Despite being characterized by the aforementioned triad, HD is classically associated with chorea, an involuntary and irregularly repetitive movement disorder that flows between various muscle groups. However, it is critical to note that chorea is not pathognomonic for HD and can be caused by a multitude of both genetic and non-genetic etiologies that requires a careful assessment of medications being used as well as family history.² It should be noted that family history may not always be reliable and clinical suspicion war-

rants further follow-up and assessment for Huntington's disease.

The onset of HD is typically characterized by imperceptible changes affecting movement and personality that may be mistaken for manifestations of other psychiatric conditions or dismissed as changes associated with aging.² As the disease progresses, these manifestations become more noticeable and disruptive to daily life. Motor involvement advances from restlessness or fidgeting to more distinct motor dysfunction, ranging from distinct chorea to ataxia, parkinsonism features, or even dysphagia.^{2,3} The psychiatric component of HD may initially present as increased irritability but will advance to more prominent symptoms of anxiety, major depression, manic episodes, apathy, and/or psychoses.¹ The severity of these psychiatric presentations will vary and are often accompanied by the third aspect of the HD triad, cognitive decline. Impairment of executive functions involving the frontal lobe are common manifestations and can disrupt tasks such as organizing, planning, and impaired problem-solving. While long-term memory is often spared during this progression, patients can suffer from significant dementia. The onset of cognitive

and psychiatric symptoms often manifest years in advance of an official diagnosis of HD.^{2,3}

Currently, there are no cures for HD despite advances in the understanding of the pathophysiology of the disease. Instead, treatment is directed at symptomatic management and counseling to ensure an enhanced quality of life, not only for the patient but the family as well. Therapeutics can be especially helpful in managing severe chorea but must be used with caution as the disease progresses due to its associated adverse effects. Historically, tetrabenazine or neuroleptic agents have been trialed but a newer drug, deutetrabenazine, received recent approval for use by the Food and Drug Administration (FDA) and shows significant upside due to its limited adverse effect profile.⁴

METHODS

We conducted literature searches using PubMed and Google Scholar between 2020-2021. Articles were chosen based on relevance to Deutetrabenazine and its therapeutic effects on chorea. We selected primary literature as well as clinical trial studies to reflect the validity of the review. Older articles were included as well to refer to previous background information.

The PubMed and Google Scholar keywords searched were as follows: Huntington's disease, chorea, Deutetrabenazine, neurodegenerative disease, and HTT gene.

HUNTINGTON'S CHOREA EPIDEMIOLOGY, PATHOPHYSIOLOGY, RISK FACTORS, AND PRESENTATION

Huntington's disease, despite being distributed worldwide, is more prevalent in certain populations. Specifically, individuals of European descent have the highest prevalence of HD, ranging from 10 to 13.7 cases per 100,000 whereas individuals of Asian or African descent have significantly lower rates of prevalence.¹⁻³ The discrepancy in prevalence amongst various ethnicities is associated with the average CAG-repeat size in the *HTT* gene, with European-descended individuals having longer repeats than those from other ethnicities.^{2,5,6} Symptom onset occurs at earlier ages in each successive generation due to the instability of the CAG repeat during replication when exceeding 28 repeats in length. The majority of these instabilities lead to expansion of the repeat, thus resulting in anticipation.²

The underlying pathophysiology of HD has not been fully elucidated; however, a number of mechanisms have been proposed with a particular emphasis on the dysfunction of the medium spiny neurons (MSNs) in the striatum.⁵ The MSNs diverge into two pathways within the striatum, the indirect and direct pathways. In the early stages of HD, the indirect pathway is particularly susceptible to the adverse effects of the mutant *HTT* gene, resulting in the characteristic hyperkinetic physical symptom of chorea. As HD progresses, involvement of the direct pathway occurs with the manifestation of hypokinetic symptoms such as akinesia and dystonia.^{6,7} Another region of interest with signif-

icance in the pathophysiology of HD is the cerebral cortex, especially in the earliest stages of the disease, where symptoms affect cognitive function more than the physical manifestations that characterize the "manifest" stage. Specific areas of the cerebral cortex that are affected are associated with the particular symptoms that patients will experience during the prodromal stages of their disease.⁷

As HD is an autosomal dominant disease, there are no risk factors that influence the likelihood of acquiring the disease or the severity of symptoms. However, multiple genome-wide association (GWA) studies have been conducted with the identification of several genes that can modify the onset of symptoms in the HD course. Specifically, genetic variations found on chromosomes 15 and 8 have been suggested to accelerate the age of onset, with a particular genetic variant on chromosome 15 being associated with a delay in the age of onset of physical symptoms.^{6,8}

Patients will often remain asymptomatic for many years with the subtle onset of symptoms often within 10-15 years prior to the "manifest" of HD.⁹ These pre-manifest symptoms classically consist of cognitive dysfunction, specifically involving executive function and multitasking. Psychiatric symptoms are also common pre-manifest symptoms experienced by patients, presenting as anxiety or irritability.² These initial changes may be so subtle that they go unnoticed by the patient and their family, but as the disease progresses towards manifest HD, these symptoms progress and slowly cause dysfunction.¹⁰ Subtle motor signs can manifest during the prodromal stage of HD and correspond with neurological changes that are detectable using MRI. These pre-manifest neurological changes correlate with the pathophysiology of HD, specifically involving MSNs of the striatum and corticostriatal connections.^{5,9} Family members may notice restlessness or fidgeting in the patient during the early stage of the disease.

As HD progresses, the severity of the triad of systems affected: cognitive, psychiatric and the motor will become more severe. Generalized slowing in cognitive function, frontal lobe dementia, and impairment of speech and swallowing will become more prominent. Speech dysfunction will begin with dysarthria but can progress to anarthria as patients move from the premanifest to manifest stage of HD. Development of dysphagia carries significant morbidity and risk for aspiration pneumonia.^{1,2,6,9} While psychiatric symptoms do not progress in a similar manner to the cognitive and motor symptoms of HD, suicidal ideation rates do increase as individuals progress from premanifest to manifest HD, and the risk continues to increase as the extent of disability increases. One other exception is apathy, which may progress in severity as a consequence of there being no specific pharmacologic therapeutic treatments for apathy, in contrast to depression or anxiety.^{2,6} The progression of motor symptoms correlates with the pathophysiology initially involving MSNs in the indirect striatal pathway followed by MSNs in the direct striatal pathway. Patients will initially display hyperkinetic motor symptoms characterized by chorea and as HD progresses,

they will develop hypokinetic symptoms, including bradykinesia, rigidity and postural impairment.^{1,6,9,10} This progression of the HD triad correlates with the progression of loss in activities of daily living (ADLs) of the patients, first affecting their occupation and eventually severely impairing the capacity to complete basic ADLs.⁹

CURRENT TREATMENT OF HUNTINGTON'S CHOREA

Current approaches to the treatment of choreiform movements in Huntington's Disease is highly varied and depend on the expertise of the treating physician. Furthermore, the initial decision to treat is also somewhat contested between experts. Given that chorea appears early during HD and then tends to attenuate as the disease progresses, most clinicians avoid treating choreiform movements unless they are particularly severe or pose a danger to the patient or caregivers.¹¹ Initially, both first- and second-generation antipsychotics were used to manage chorea in HD.¹² The questionable efficacy of the neuroleptics, as well as their significant negative side effect profile, necessitated the discovery of better pharmacologic therapies to alleviate chorea.¹² Newer additions for the treatment of chorea include the vesicular monoamine transporter (VMAT2) inhibitor tetrabenazine, anti-NMDA drugs such as amantadine, and non-pharmacologic approaches such as deep brain stimulation (DBS). Each of these options is discussed below.

ANTIPSYCHOTICS

All neuroleptic agents are antagonists of the dopamine receptors in the central nervous system with the exception of aripiprazole, a partial dopamine receptor agonist.¹¹ These drugs were historically the first-line treatment for the positive movement symptoms of HD. As chorea is thought to be a result of an excess of dopamine in the basal ganglia, antipsychotics were thought to be a reasonable option.¹³ There have been surprisingly few studies focused on the use of neuroleptics in the treatment of chorea in HD, most likely due to the reluctance of pharmaceutical companies to invest in studies that do not yield new therapeutic patents.¹⁴ The few trials that exist show a dubious benefit of neuroleptics. Typical antipsychotics such as haloperidol and fluphenazine have received mixed reviews in chorea reduction but continue to be prescribed by some clinicians. Similarly, the atypical antipsychotics (which carry the benefit of a milder side effect profile than their first-generation counterparts) have failed to produce strong evidence to support their use in treating choreiform movements.¹⁵ Research has provided the strongest evidence that olanzapine, risperidone, clozapine, and quetiapine improve choreiform movements in HD. However, the risk of severe side effects such as agranulocytosis associated with clozapine, as well as the low affinity of clozapine and quetiapine for dopamine receptors limit their use.¹⁶ Regardless of the lack of evidence, antipsychotics are still an option for patients

with HD who desire a reduction in chorea and are highly favored in patients that have comorbid psychosis.¹¹

TETRABENAZINE

Tetrabenazine (TBZ) was the first drug to earn FDA approval in the treatment of chorea associated with HD and was the only drug to have this indication until deutetrabenazine was approved in 2017. TBZ inhibits VMAT2, leading to reduced monoamine loading into presynaptic vesicles.⁷ The overall effect is a drop in synaptic levels of monoamines, particularly dopamine, serotonin, and norepinephrine.¹⁶ TBZ revolutionized the treatment of chorea and has the strongest evidence backing its use.¹² The main downside to TBZ is the side effect profile. TBZ carries a risk of the neuroleptic malignant syndrome and QTc prolongation, also noted with antipsychotics.¹² Of note, the reduction in serotonin may cause a worsening of depressive symptoms and suicidality, which can both be present already in patients with HD.¹⁶ TBZ received a black box warning for this reason and is contraindicated in patients who are actively suicidal or have untreated depression.¹⁵ Finally, as it is a newer treatment, TBZ can be rather costly, removing it as an option for many patients.¹⁶

AMANTADINE

Amantadine is a known NMDA receptor antagonist that has shown useful in treating abnormal movements in Parkinson's disease. It has also been shown to have effects on dopaminergic pathways in the brain, although these are not well understood.¹⁵ The effects of amantadine on dopamine in the central nervous system created hopes that it could be an effective treatment for chorea in HD. Once again, there is a paucity of studies looking at amantadine for the treatment of chorea. Studies have shown that choreiform movements are attenuated only with very high doses. These high doses are associated with a side effect profile that limits the use of amantadine for chorea treatment.¹²

DBS

In terms of a non-pharmacological approach, deep brain stimulation has shown promise in the treatment of chorea in HD, particularly in refractory cases.¹⁵ DBS trials have shown benefits with targeting the globus pallidus internal, with short-term as well as a sustained reduction in choreiform movements with minimal adverse effects.¹⁷

Many of the other interventions studied showed minimal or no benefit in treating chorea. Interestingly, the anti-glutamate drug riluzole has been endorsed as beneficial by the American Academy of Neurology (AAN), however, no definitive studies demonstrate a reduction in choreiform movements.¹⁸ Decisions of whether or not to treat chorea and which treatment route to pursue are a discussion between the physician, the patient, and caregivers.¹²

DEUTETRABENAZINE DRUG INFO

Deutetrabenazine (AUSTEDO) received approval in 2017 with an indication for tardive dyskinesia and choreiform movement in HD. It is manufactured by Teva Pharmaceuticals USA, Inc.¹⁹ Deutetrabenazine is the product of deuteration— that is, replacing certain hydrogen atoms with deuterium, an isotope of hydrogen that contains a proton and a neutron. Austedo is the deuterated form of tetrabenazine, which is the original drug indicated for the treatment of chorea.²⁰ Austedo has a molecular weight of 323.46 with a pKa of 6.31. Deutetrabenazine comes in oral formulations of 6, 9, and 12 mg.¹⁹

Deutetrabenazine carries a number of reported side effects. Some of the most reported side effects include xerostomia, diarrhea, fatigue, and sedation. While the most concerning side effect of tetrabenazine was an increase in suicidal ideation and depression, studies showed that deutetrabenazine had little to no increase in both depression and suicidal thoughts.¹⁶ Given that more studies into the safety of deutetrabenazine need to be completed, deutetrabenazine is still not recommended for patients with active suicidal ideation or a history of untreated depression.¹⁹ Deutetrabenazine may also increase the QTc interval, increasing the risk of causing deadly cardiac arrhythmias such as torsades de pointes. Assessment of a patient's QTc interval via EKG should be performed before as well as during treatment with deutetrabenazine, especially if the patient needs a dose above 24 mg. Deutetrabenazine is also contraindicated in patients who are taking MAOIs, tetrabenazine, and valentine, as well as those who have liver impairment.¹⁹ While unlikely, it has been reported that deutetrabenazine carries a risk of inducing neuroleptic malignant syndrome.²¹

The starting dose of deutetrabenazine in patients with HD is 6 mg. The dose is an oral administration given once a day. Doses should be titrated up by 6 mg per week until symptoms resolve, or side effects become intolerable.¹⁹ The maximum dose of deutetrabenazine is 48 mg per day, which is given as 24 mg twice per day. The maximum dose is reduced to 36 mg per day in patients who are designated as poor CYP2D6 metabolizers and those who are taking strong CYP2D6 inhibitors (such as paroxetine or fluoxetine).²¹ Deutetrabenazine does not need to be tapered down in the event of discontinuation and can be restarted at the current dose should the administration be interrupted for less than a week. In the event that deutetrabenazine is stopped for greater than one week, dosages should be re-titrated if resumed. It is recommended that deutetrabenazine be taken with food.¹⁹

MECHANISM OF ACTION

Deutetrabenazine is the deuterated form of the chorea treatment drug tetrabenazine. As such, it is hypothesized that it functions in a similar manner to tetrabenazine. The exact mechanism of both drugs is not completely understood, but evidence points to a reversible, inhibitory effect on the vesicular monoamine transporter, VMAT2.²² Func-

tionally, VMAT2 works presynaptically to package the monoamines (e.g., norepinephrine, serotonin, and dopamine) into vesicles to be released into the synapse when an action potential reaches the nerve terminal. By blocking the action of VMAT2, deutetrabenazine can effectively reduce the levels of monoamines in the synaptic cleft.²³ Levels of monoamines are further reduced due to the fact that they are rapidly metabolized by monoamine oxidase (MAO) in the presynaptic neuron when not packaged into vesicles. Inhibiting VMAT2 also reduces the uptake of monoamines back into the presynaptic neuron.²⁴ It is this decrease in monoamine levels, especially dopamine, that is thought to be therapeutic in the treatment of chorea in HD.¹⁴

The decrease in monoamine levels in the synaptic cleft also accounts for deutetrabenazine's side effect profile. The potential for increased depression and suicidal ideation is suggested to be from the decrease in serotonin levels in the central nervous system. Somnolence, as well as the risk of a neuroleptic malignant syndrome, are both side effects common to antipsychotics, which antagonize dopamine in the central nervous system. As deutetrabenazine has a similar mechanism of action to antipsychotics, these side effects are anticipated and seen clinically. Of note, many described adverse risks from deutetrabenazine come from experiences with the original drug tetrabenazine, and not from dedicated studies of deutetrabenazine.²⁵

PHARMACOKINETICS/PHARMACODYNAMICS

Deutetrabenazine has a chemical structure similar to the drug tetrabenazine, however, there are six atoms of deuterium in place of hydrogen, three on carbon 9 and two on carbon 10.²⁵ The effects of deuteration is the stabilization of the molecule while retaining its reactivity.²⁶ Deutetrabenazine is extensively absorbed after oral administration, with at least 80% of the drug being taken up.¹⁹ It is quickly metabolized in hepatic microsomes by carbonyl reductase to produce two main active metabolites: α -HTBZ and β -HTZB that antagonize VMAT2 in the central nervous system. Peak concentrations of the active metabolites are reached between three and four hours after administration. According to radioactive studies, both active metabolites are extensively distributed to the brain and reach their highest concentrations in the striatal tissue; the lowest concentrations were found in the cortex. The active metabolites are mainly biotransformed by the liver enzyme CYP2D6 via glucuronidation, oxidation, and sulfation; ultimately, they are excreted by the kidneys.²⁵

The effects of deuteration on the pharmacokinetics of deutetrabenazine are interesting, and they show promise that deuteration can be used to improve many current pharmacological treatments in any number of disorders. In addition to the stabilization of the molecule, deuteration creates a drug that is more resistant to metabolism by the body.²⁷ This is thought to be the result of the fact that the carbon-deuterium bond is much stronger than the carbon-hydrogen bond: studies show it is around eight times stronger.²⁵ The resulting effect is that the breakdown of the

active metabolites by the CYP2D6 enzyme is slowed. Interestingly, the strategic placement of the deuterium atoms in the molecule leads to no effect on the reduction of deutetrabenazine into the active metabolites, α -HTBZ and β -HTBZ.²⁷ As a result, studies showed that the half-life of the active metabolites was doubled with deutetrabenazine as compared to tetrabenazine, with no increase in peak plasma concentrations of active metabolites.²⁵ As this points to an increase in exposure time to active metabolites, evidence suggests the possibility that deutetrabenazine can provide the same therapeutic benefit as tetrabenazine with a lower dose.²⁸ In addition, the increased half-life of active metabolites results in a twice-a-day dosing for deutetrabenazine compared to thrice-a-day dosing for tetrabenazine.²⁶ Given the dose-dependent side effect profile of both drugs and the difficulties in adherence to a schedule of multiple doses per day, deutetrabenazine shows promise as a better alternative for chorea treatment.

CLINICAL STUDIES: SAFETY AND EFFICACY

The clinical effectiveness of Deutetrabenazine as a treatment for chorea among patients with Huntington's Disease (HD) was evaluated in a randomized, double-blind, placebo-controlled, parallel-group study done by the Huntington Study Group known as First-HD. This study took place at 34 sites in the United States and Canada and consisted of 90 patients randomized into two groups. Patients that had a baseline score of 8 or greater for total maximal chorea (TMC) of the Unified Huntington Disease Rating Scale (UHDRS) and a screening score of 5 or greater for UHDRS total functional capacity. The TMC score relates to the severity of chorea, with higher scores equating with more severe cases of chorea in patients with HD. Patients suffering from serious un/undertreated psychiatric illnesses were excluded, however, patients on a successful maintenance dose of medication for psychiatric illnesses such as depression were still included. Patients with a history of suicidal thoughts or behaviors were excluded. Conditions that also excluded patients from this study included a prolonged QTc interval as well as patients taking medication potentially able to prolong the QT interval, left bundle branch block, hepatic impairment, renal impairment, as well as patients who received a score of 11 and higher on the Swallowing Disturbance Questionnaire. Patients were randomized 1:1 with Half of the patients, $n=45$, given deutetrabenazine and the other group, $n=45$, of patients receiving the placebo. The time span of the study was 12 weeks, the first 8 weeks consisting of a dose-titration period and the remaining 4 weeks being a maintenance phase. Endpoints chosen as measures of primary efficacy were changes in TMC score from baseline during the maintenance phase. Secondary efficacy endpoints consisted of 3 parts, the Patient Global Impression of Change (PGIC) score, the Clinical Global Impression of Change (CGIC) score, and a 36-item Short-Form Health Survey (SF-36) physical functioning subscale score. Safety Outcomes were measured through changes from baseline to the end of the maintenance phase. These included the Barnes Akathisia

Rating Scale, Epworth Sleepiness Scale, UPDRS speech score, Montreal Cognitive Assessment, HADS depressions, and anxiety subscale. This study was not designed to investigate adverse events and as such further investigation is needed to draw more definitive conclusions on the safety of deutetrabenazine.²⁹ As compared to placebo from baseline to maintenance, patients in the deutetrabenazine group had a mean of -4.4 (95% CI) improvement in TMC score versus a mean of -1.9 (95% CI) improvement in TMC score in the placebo group with a significant treatment difference of -2.5 (95%CI, $p<0.001$).³⁰

The same group that performed the FIRST-HD Trial, the Huntington Group, as well as the Alternatives for Reducing Chorea in Huntington Disease investigators (ARC-HD) performed another study evaluating the safety of converting from tetrabenazine to deutetrabenazine for the treatment of chorea. This was a small open-label, single-arm study that enrolled 37 patients ($n=37$) from sites in the United States and Australia. Patients participating in the study had received therapeutic relief from the doses of tetrabenazine they were already prescribed. The patients were then switched to deutetrabenazine therapy overnight and titration of deutetrabenazine doses occurred weekly after the first week to optimize control of the chorea. Initially, the median daily dose of deutetrabenazine was 18mg, and after adjustments the median dose at week 4 was 30mg and 36mg at week 8. They evaluated changes from baseline in patient's Unified Huntington Disease Rating Scale (UHDRS) total maximal chorea score (TMC) and total motor score (TMS). Higher scoring indicates more pronounced motor signs. Safety outcomes were measured as adverse events reported by the patients. Treatment emergent adverse events (TEAEs), include but are not limited to somnolence, falls, nasopharyngitis, anxiety, diarrhea, constipation, dry mouth, depression, and irritability. TEAEs occurred in at least 4% of patients with 54% of patients reporting at least 1 TEAE.³¹

The study known as AIM-TD was a double-blind, randomized, placebo-controlled, phase 3 trial aimed at assessing the clinical efficacy, safety, and tolerability of fixed doses of Deutetrabenazine as a treatment for the involuntary movements in patients with tardive dyskinesia. The involuntary movements seen in tardive dyskinesia may be more accurately described as chorea, though they also include stereotypy and/or dystonia.³² AIM-TD was conducted at various participating centers in the United States and Europe at 75 centers. Participating patients ($n=298$) were randomized (1:1:1:1) into 4 groups; patients receiving at least one dose of the placebo ($n=74$), patients receiving 12mg per day of deutetrabenazine ($n=75$), patients receiving 24mg per day ($n=74$), and patients receiving 36mg/day ($n=75$). The primary endpoint for efficacy was a change in the Abnormal Involuntary Movement Scale (AIMS) score from baseline to week 12. The 36mg per day group had a treatment difference of -1.9 points of the AIMS score (95%CI, $p=0.001$), and the 24 mg per day group had a treatment difference of -1.8 points of the AIMS score ($p=0.003$) versus the placebo group with a difference of -1.4 points. Reported incidence of AEs were similar between placebo

and deutetrabenazine groups. Rates of nervous system adverse events of interest such as akathisia, dyskinesia, headache, migraine, parkinsonism, sedation, and somnolence were recorded. Patients in the 36mg/day group experienced a proportion of nervous system AEs greater than the 12mg/day and 24mg/day groups which were more similar to the placebo rates.³³

Tetrabenazine has been shown to improve the symptoms of chorea associated with HD, but the adverse effects associated with tetrabenazine have raised concern amongst patients and physicians. Adverse events (AE)s include, but are not limited to, agitation, akathisia, anxiety, coughing, depression, diarrhea, drowsiness/somnolence, falls, fatigue, insomnia, nausea, parkinsonism, and vomiting. In a retrospective study performed by Claassen *et al.* unadjusted and adjusted analyses showed that deutetrabenazine versus tetrabenazine was associated with a significantly lower risk of AEs. The researchers utilized data from the First-HD trial and the TETRA-HD trial and conducted an indirect treatment comparison of the tolerability of deutetrabenazine versus tetrabenazine using two anchor-based methods: Bucher comparison for unadjusted data and matching indirect comparison for adjusted data. Deutetrabenazine demonstrated significantly lower rates for overall AEs and moderate to severe AEs than tetrabenazine ($p < 0.001$). The resulting risk for moderate to severe AEs in the unadjusted (-39.6%, 95% CI: -67.1, -12.2%; $p = 0.005$) and adjusted (-46%, 95% CI: -79.4, -13.3%; $p = 0.006$) analyses with deutetrabenazine compared to tetrabenazine. According to their analyses, overall dose reductions due to AEs occurred less frequently with deutetrabenazine as compared with tetrabenazine before and after adjustment for placebo ($p < 0.001$).³⁴

Rodrigues *et al.* compared deutetrabenazine to tetrabenazine indirectly using meta-analytical methods. They used the results of the TETRA-HD trial and the FIRST-HD trial, as they considered both studies as methodologically and clinically similar enough for comparison. Their assessment as to the confidence in the evidence was according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working group guidelines. The indirect comparison according to GRADE showed low quality evidence that tetrabenazine and deutetrabenazine do not differ in their clinical efficacy and safety. They found that deutetrabenazine appeared significantly less likely to cause somnolence and depressive symptoms, but they cautioned against extrapolating the results of the indirect comparison. No head-to-head randomized blinded trial has been performed comparing the adverse events related to deutetrabenazine versus tetrabenazine for the treatment of HD-related chorea.³⁵

Claassen *et al.* gave an expert opinion in a review of clinical trial data on Deutetrabenazine for tardive dyskinesia and chorea associated with HD. They reviewed the clinical efficacy, safety, and pharmacokinetics in Phase III and long-term extension studies with an emphasis on the long-term safety and tolerability of deutetrabenazine. Their review concluded that regardless of disease severity, deutetrabenazine was tolerated well and effective in long-

term treatment. It highlighted the importance of addressing the risk of treatment-emergent depression and suicidality. Providers need to consider the black box warnings for AEs such as depression and suicide associated with Vesicular Monoamine Transporter 2 (VMAT2) inhibitors and need to be carefully monitored for these symptoms. They concluded that patients with tardive dyskinesia treated with deutetrabenazine had significant reductions in their tardive dyskinesia involuntary movement score.³⁶

Deutetrabenazine's pharmacologic properties, drug interactions, administration, and efficacy of administration was reviewed by Richard *et al.* As was highlighted by several reviews, they also noted there are still no direct comparisons between treatments for tardive dyskinesia. The problem remains that no direct head-to-head comparisons of VMAT2 inhibitors such as tetrabenazine and deutetrabenazine exist. They also conclude both tetrabenazine and deutetrabenazine administration statistically significantly improves chorea as compared to placebo and adverse effects were comparable to placebo.²⁹

Another review evaluating the clinical efficacy and safety of a deuterated analog of tetrabenazine in the First-HD study and ARC-HD study by Bashir *et al.* found that the results from both studies demonstrated that oral deutetrabenazine is generally safe, well-tolerated, and efficacious.²⁵

The main studies investigating deutetrabenazine for the treatment of chorea are the First-HD clinical trial, the ARC-HD clinical trial, and the two indirect comparison studies. The objective of the First-HD clinical trial was to evaluate deutetrabenazine versus placebo in the treatment of chorea. The main conclusion that can be drawn from the FIRST-HD trial is that it showed a statistically significant improvement in chorea in patients taking deutetrabenazine versus placebo. The major drawback of this study was the lack of head-to-head comparisons of treatment-emergent adverse events of deutetrabenazine to other VMAT2 inhibitors for the treatment of chorea in HD. The ARC-HD clinical trial's objective was to evaluate the safety and efficacy of conversion from tetrabenazine to deutetrabenazine in an open-label switch overnight from their current dose to tetrabenazine to deutetrabenazine. This trial found no worsening symptoms of HD after the overnight conversion and found a similar side effect profile for deutetrabenazine when compared with the First HD.

Indirect comparison studies have resulted in conflicting conclusions on the safety of deutetrabenazine versus tetrabenazine. Claassen *et al.* performed an indirect comparison study comparing deutetrabenazine with tetrabenazine with respect to adverse events. The data was sourced from the First-HD and Tetra-HD trials. They found an overall lower risk difference for adverse events with deutetrabenazine and that there was better medication adherence with deutetrabenazine compared with tetrabenazine. However, the results of this indirect comparison have come into question, with concern for lack of clinically meaningful difference versus statistically significant results. The indirect comparison meta-analysis performed by Rodrigues *et al.* compared the tolerability of deutetrabenazine versus tetrabenazine for safety and adverse events. Their meta-analysis

Table 1. Clinical Efficacy and Safety

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Frank et al (2017) First-HD	99 patients with HD randomized to receive deutetrabenazine or placebo in a double blinded study	TMC mean scores decreased from baseline to maintenance treatment by 4.4 points vs 1.9 points with placebo ($P < .001$).	Deutetrabenazine versus placebo resulted in improvement of chorea at 12 week.
Frank et al. (2017) ARC-HD	37 patients with chorea associated with HD switched overnight from stable tetrabenazine regimen to deutetrabenazine. This was an open-label, single arm study.	Deutetrabenazine was generally safe and well tolerated. Chorea scores maintained at week 1 and improved at week 8.	Chorea scores did not worsen after the overnight switch to deutetrabenazine. Adverse events and side effects were like what was seen in First-HD

did not demonstrate any differences between the two medications. These authors critique the indirect comparison study performed by Claassen *et al.* stating readers should be aware of the potential for discrepant findings potentially arising from the rank reversal phenomenon. The meta-analysis suggests that risk differences increase interpretability, but emphasizes odds ratios are the only statistic able to guarantee to avoid impossible predicted event rates when extrapolating the data for the population at large.³⁷

Given the dearth of current information directly comparing the clinical efficacy and safety of deutetrabenazine versus other VMAT2 inhibitors, there is a clear need for direct head-to-head clinical trials. Several clinical reviews comparing the clinical efficacy and safety of deutetrabenazine versus tetrabenazine as well as an analysis of current literature show the need for direct comparison of the medication.^{15,37–39} While the pharmacokinetics of deutetrabenazine give hope for its reduced toxicity, more information and direct studies are needed to evaluate the true long-term safety and efficacy of deutetrabenazine versus other medications.²⁹

Providers considering prescribing this medication should make sure to consult the medication label as there are listed contraindications and warnings for deutetrabenazine. Contraindications for deutetrabenazine include suicidality, undertreated or untreated depression, hepatic impairment, and patients current taking monoamine oxidase inhibitors (MAOI), reserpine, or tetrabenazine. Clinical efficacy and safety, along with comparative studies are summarized in Tables 1 and 2.

CONCLUSION

Huntington's disease is a progressively disabling and ultimately fatal neurodegenerative disorder with autosomal dominant inheritance. Characterized by a triad of cognitive, psychiatric, and motor symptoms that largely increase in severity as the disease progresses, HD can be significantly disabling for patients. With no definitive cure available, treatment is directed at symptomatic management to improve the quality of life. Deutetrabenazine, which recently

received FDA approval for the treatment of HD-associated chorea, is one such therapy. A VMAT-2 inhibitor consisting of deuterium substituted for hydrogen at various key positions in the tetrabenazine molecule results in a longer half-life and decreased dosing requirements, deutetrabenazine provides a therapeutic improvement in the severity of chorea and, subsequently, quality of life. However, there remains a deficit of knowledge regarding the overall efficacy of deutetrabenazine compared to tetrabenazine. Preliminary meta-analyses of indirect comparison studies have provided conflicting and inconclusive data, thus necessitating the need for a direct head-to-head study. Nonetheless, the development of novel therapeutics such as deutetrabenazine offers patients an opportunity to enhance their quality of life by targeting the disruptive motor symptom of chorea that is characteristic of HD.

Submitted: December 13, 2021 EST, Accepted: January 03, 2022 EST

Table 2. Comparative Studies

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Claassen et al. 2017 Indirect tolerability comparison of Deutetrabenazine and Tetrabenazine for Huntington disease	Indirect comparison analysis between Tetra-HD and First-HD. Comparison between deutetrabenazine and tetrabenazine for patient outcomes and adverse events	Deutetrabenazine as compared to tetrabenazine was associated with significantly lower risk of moderate to severe adverse events (akathisia, depression, somnolence, insomnia, and parkinsonism). Deutetrabenazine had significantly lower rate of dose reduction or suspension.	Deutetrabenazine is more tolerable than tetrabenazine for the treatment of HD associated chorea.
Rodrigues et al. (2017) Tetrabenazine Versus Deutetrabenazine for Huntington's Disease: Twins or Distant Cousins?	Indirect comparison using meta analytical methods. Tetra-HD and First-HD. Comparison between deutetrabenazine and tetrabenazine for efficacy.	Participants from both groups did not differ significantly on motor scores or adverse events.	Tetrabenazine and deutetrabenazine do not differ in efficacy in reducing motor scores.

REFERENCES

1. Walker RH. Chorea. *CONTINUUM*. 2013;19:1242-1263. [doi:10.1212/01.con.0000436155.46909.c3](https://doi.org/10.1212/01.con.0000436155.46909.c3)
2. Walker FO. Huntington's disease. *Lancet*. 2007;369(9557):218-228. [doi:10.1016/s0140-6736\(07\)60111-1](https://doi.org/10.1016/s0140-6736(07)60111-1)
3. Cardoso F. Huntington Disease and Other Choreas. *Neurologic Clinics*. 2009;27(3):719-736. [doi:10.1016/j.ncl.2009.04.001](https://doi.org/10.1016/j.ncl.2009.04.001)
4. Dean M, Sung V. Review of deutetrabenazine: a novel treatment for chorea associated with Huntington's disease. *Drug Des Dev Ther*. 2018;12:313-319. [doi:10.2147/dddt.s138828](https://doi.org/10.2147/dddt.s138828)
5. Snowden JS. The Neuropsychology of Huntington's Disease. *Arch Clin Neuropsychol*. 2017;32(7):876-887. [doi:10.1093/arclin/acx086](https://doi.org/10.1093/arclin/acx086)
6. McColgan P, Tabrizi SJ. Huntington's disease: a clinical review. *Eur J Neurol*. 2018;25(1):24-34. [doi:10.1111/ene.13413](https://doi.org/10.1111/ene.13413)
7. Raymond LA, André VM, Cepeda C, Gladding CM, Milnerwood AJ, Levine MS. Pathophysiology of Huntington's disease: time-dependent alterations in synaptic and receptor function. *Neuroscience*. 2011;198:252-273. [doi:10.1016/j.neuroscience.2011.08.052](https://doi.org/10.1016/j.neuroscience.2011.08.052)
8. Lee JM, Wheeler VC, Chao MJ, et al. Identification of Genetic Factors that Modify Clinical Onset of Huntington's Disease. *Cell*. 2015;162(3):516-526. [doi:10.1016/j.cell.2015.07.003](https://doi.org/10.1016/j.cell.2015.07.003)
9. Ghosh R, Tabrizi SJ. Clinical features of huntington's disease. In: *Advances in Experimental Medicine and Biology*. Springer International Publishing; 2018:978-973. https://doi.org/10.1007/978-3-319-71779-1_1
10. Jankovic J, Roos RAC. Chorea associated with Huntington's disease: to treat or not to treat? *Mov Disord*. 2014;29(11):1414-1418. [doi:10.1002/mds.25996](https://doi.org/10.1002/mds.25996)
11. Coppen EM, Roos RAC. Current Pharmacological Approaches to Reduce Chorea in Huntington's Disease. *Drugs*. 2017;77(1):29-46. [doi:10.1007/s40265-016-0670-4](https://doi.org/10.1007/s40265-016-0670-4)
12. Suchowersky O, Armstrong MJ, Miyasaki J. Evidence-based guideline: pharmacologic treatment of chorea in Huntington disease: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2013;80(10):970-970. [doi:10.1212/wnl.0b013e3182885eb3](https://doi.org/10.1212/wnl.0b013e3182885eb3)
13. Sung VW, Iyer RG, Gandhi SK, et al. Physician perceptions of pharmacologic treatment options for chorea associated with Huntington disease in the United States. *Curr Med Res Opin*. 2018;34(4):643-648. [doi:10.1080/03007995.2018.1435518](https://doi.org/10.1080/03007995.2018.1435518)
14. Schmidt C. First deuterated drug approved. *Nat Biotechnol*. 2017;35(6):493-494. [doi:10.1038/nbt0617-493](https://doi.org/10.1038/nbt0617-493)
15. Bashir H, Jankovic J. Deutetrabenazine for the treatment of Huntington's chorea. *Expert Rev Neurother*. 2018;18(8):625-631. [doi:10.1080/14737175.2018.1500178](https://doi.org/10.1080/14737175.2018.1500178)
16. Wyant KJ, Ridder AJ, Dayalu P. Huntington's Disease—Update on Treatments. *Curr Neurol Neurosci Rep*. 2017;17(4):1-11. [doi:10.1007/s11910-017-0739-9](https://doi.org/10.1007/s11910-017-0739-9)
17. Edwards TC, Zrinzo L, Limousin P, Foltynie T. Deep brain stimulation in the treatment of chorea. *Mov Disord*. 2012;27(3):357-363. [doi:10.1002/mds.23967](https://doi.org/10.1002/mds.23967)
18. Reilmann R. Pharmacological treatment of chorea in Huntington's disease—good clinical practice versus evidence-based guideline. *Mov Disord*. 2013;28(8):1030-1033. [doi:10.1002/mds.25500](https://doi.org/10.1002/mds.25500)
19. Drugs@FDA: FDA-Approved Drugs. Accessed December 5, 2021. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=209885>
20. Schmidt C. First deuterated drug approved. *Nat Biotechnol*. 2017;35(6):493-494. [doi:10.1038/nbt0617-493](https://doi.org/10.1038/nbt0617-493)
21. Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Published April 2, 2019. Accessed December 5, 2021. <https://www.ncbi.nlm.nih.gov/books/NBK548187/>
22. Niemann N, Jankovic J. Real-world experience with VMAT2 inhibitors. *Clin Neuropharm*. 2019;42(2):37-41. [doi:10.1097/wnf.0000000000000326](https://doi.org/10.1097/wnf.0000000000000326)

23. Jankovic J. Dopamine depleters in the treatment of hyperkinetic movement disorders. *Expert Opin Pharmacother*. 2016;17(18):2461-2470. [doi:10.1080/14656566.2016.1258063](https://doi.org/10.1080/14656566.2016.1258063)
24. Carvedilol Therapy and CYP2D6 Genotype - PubMed. Accessed December 6, 2021. <https://pubmed.ncbi.nlm.nih.gov/30067327/>
25. Bashir H, Jankovic J. Deutetrabenazine for the treatment of Huntington's chorea. *Expert Rev Neurother*. 2018;18(8):625-631. [doi:10.1080/14737175.2018.1500178](https://doi.org/10.1080/14737175.2018.1500178)
26. Russak EM, Bednarczyk EM. Impact of Deuterium Substitution on the Pharmacokinetics of Pharmaceuticals. *Ann Pharmacother*. 2019;53(2):211-216. [doi:10.1177/1060028018797110](https://doi.org/10.1177/1060028018797110)
27. Schneider F, Bradbury M, Baillie TA, et al. Pharmacokinetic and Metabolic Profile of Deutetrabenazine (TEV-50717) Compared With Tetrabenazine in Healthy Volunteers. *Clin Transl Sci*. 2020;13(4):707-717. [doi:10.1111/cts.12754](https://doi.org/10.1111/cts.12754)
28. DeWitt SH, Maryanoff BE. Deuterated Drug Molecules: Focus on FDA-Approved Deutetrabenazine. *Biochemistry*. 2018;57(5):472-473. [doi:10.1021/acs.biochem.7b00765](https://doi.org/10.1021/acs.biochem.7b00765)
29. Richard A, Frank S. Deutetrabenazine in the treatment of Huntington's disease. *Neurodegener Dis Manag*. 2019;9(1):31-37. [doi:10.2217/nmt-2018-0040](https://doi.org/10.2217/nmt-2018-0040)
30. Frank S, Testa CM, Stamler D, et al. Effect of Deutetrabenazine on Chorea Among Patients With Huntington Disease: A Randomized Clinical Trial. *JAMA*. 2016;316(1):40-50. [doi:10.1001/jama.2016.8655](https://doi.org/10.1001/jama.2016.8655)
31. Frank S, Stamler D, Kayson E, et al. Safety of Converting From Tetrabenazine to Deutetrabenazine for the Treatment of Chorea. *JAMA Neurol*. 2017;74(8):977-982. [doi:10.1001/jamaneurol.2017.1352](https://doi.org/10.1001/jamaneurol.2017.1352)
32. Walker RH. Chorea. *CONTINUUM*. 2013;19:1242-1263. [doi:10.1212/01.con.0000436155.46909.c3](https://doi.org/10.1212/01.con.0000436155.46909.c3)
33. Anderson KE, Stamler D, Davis MD, et al. Deutetrabenazine for treatment of involuntary movements in patients with tardive dyskinesia (AIM-TD): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Psychiatry*. 2017;4(8):595-604. [doi:10.1016/s2215-0366\(17\)30236-5](https://doi.org/10.1016/s2215-0366(17)30236-5)
34. Claassen DO, Carroll B, de Boer LM, et al. Indirect tolerability comparison of Deutetrabenazine and Tetrabenazine for Huntington disease. *J Clin Mov Disord*. 2017;4(1). [doi:10.1186/s40734-017-0051-5](https://doi.org/10.1186/s40734-017-0051-5)
35. Rodrigues FB, Duarte GS, Costa J, Ferreira JJ, Wild EJ. Tetrabenazine Versus Deutetrabenazine for Huntington's Disease: Twins or Distant Cousins? *Mov Disord Clin Pract*. 2017;4(4):582-585. [doi:10.1002/mdc3.12483](https://doi.org/10.1002/mdc3.12483)
36. Claassen DO, Philbin M, Carroll B. Deutetrabenazine for tardive dyskinesia and chorea associated with Huntington's disease: a review of clinical trial data. *Expert Opin Pharmacother*. 2019;20(18):2209-2221. [doi:10.1080/14656566.2019.1674281](https://doi.org/10.1080/14656566.2019.1674281)
37. Rodrigues FB, Duarte GS, Costa J, Ferreira JJ, Wild EJ. Meta-research metrics matter: letter regarding article "indirect tolerability comparison of Deutetrabenazine and Tetrabenazine for Huntington disease." *J Clin Mov Disord*. 2017;4(1):1-3. [doi:10.1186/s40734-017-0067-x](https://doi.org/10.1186/s40734-017-0067-x)
38. Dean M, Sung V. Review of deutetrabenazine: a novel treatment for chorea associated with Huntington's disease. *Drug Des Dev Ther*. 2018;12:313-319. [doi:10.2147/dddt.s138828](https://doi.org/10.2147/dddt.s138828)
39. Rodrigues FB, Wild EJ. Huntington's Disease Clinical Trials Corner: February 2018. *J Huntington's Dis*. 2018;7(1):89-98. [doi:10.3233/jhd-189001](https://doi.org/10.3233/jhd-189001)